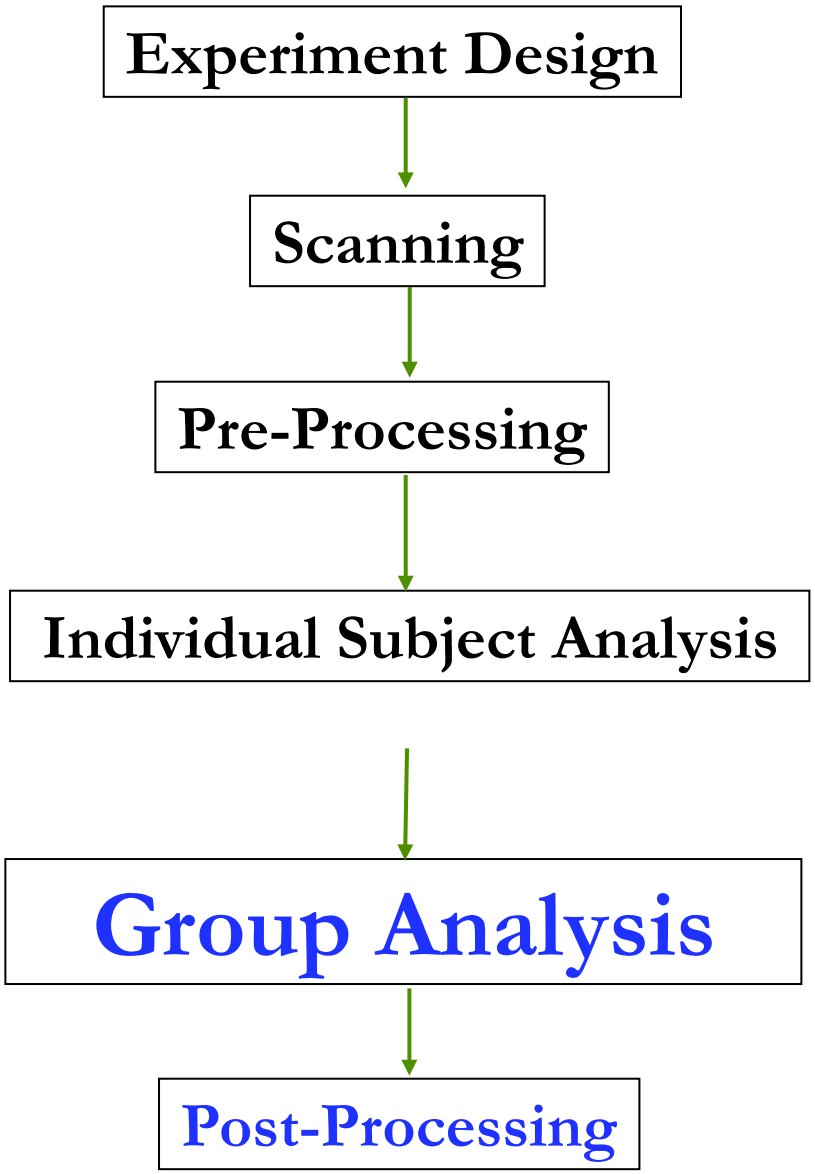
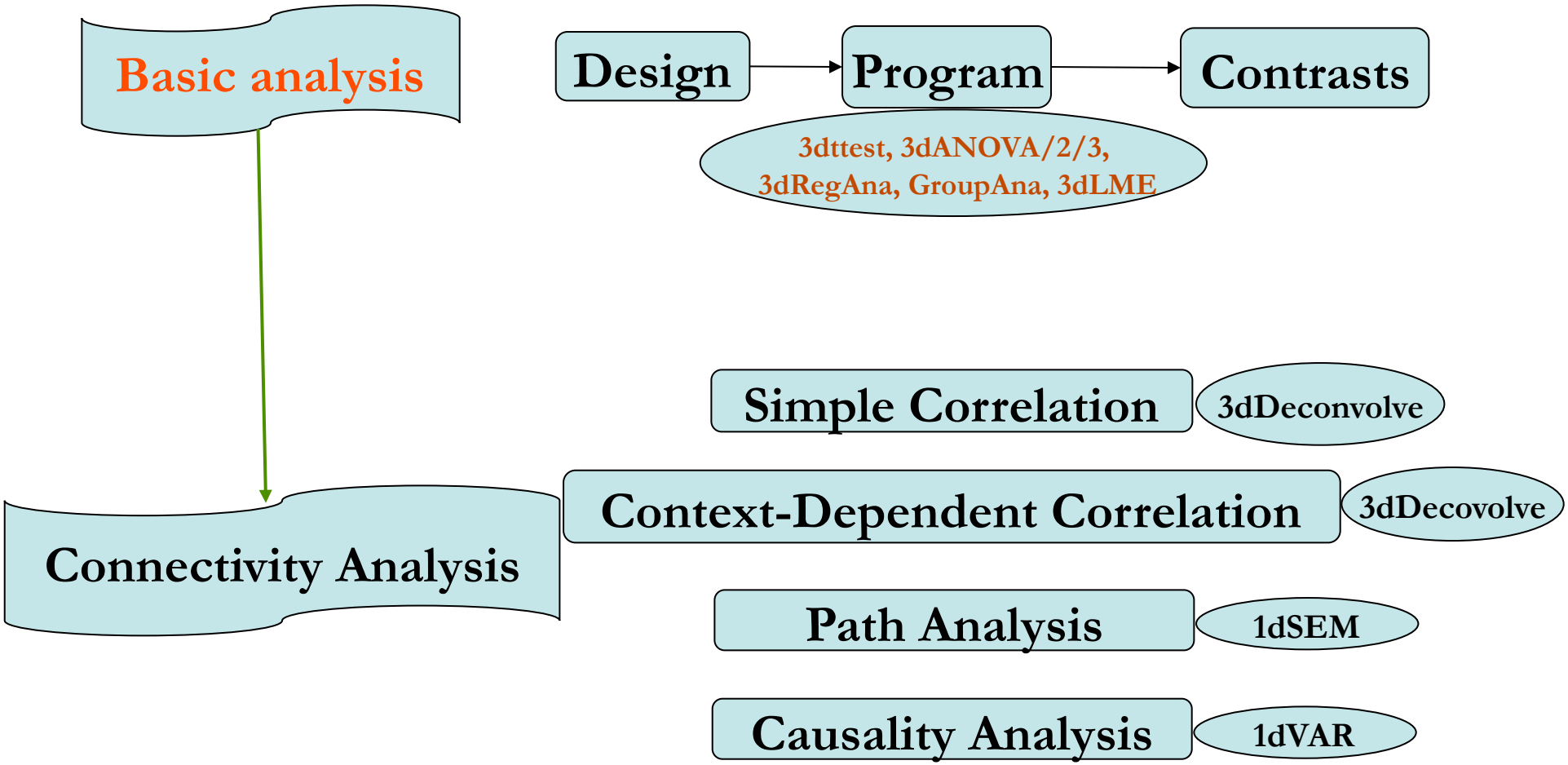
FMRI Analysis



Group Analysis



- **Group Analysis: Why and how?**
  - Group analysis
    - Make general conclusions about some population, *e.g.*,
      - Do men and women differ on responding to fear?
      - What regions are related to happiness, sad, love, faith, empathy, etc.?
      - What differs when a person listens to classical music vs. rock 'n' roll?
    - Partition/untangle data variability into various effects
  - Why two tiers of analysis: individual and then group?
    - No perfect approach to combining both into a batch analysis
    - Each subject may have slightly different design or missing data
    - High computation cost
    - Usually we take β's (% signal change) to group analysis
      - Within-subject variation relatively small compared to cross-subject

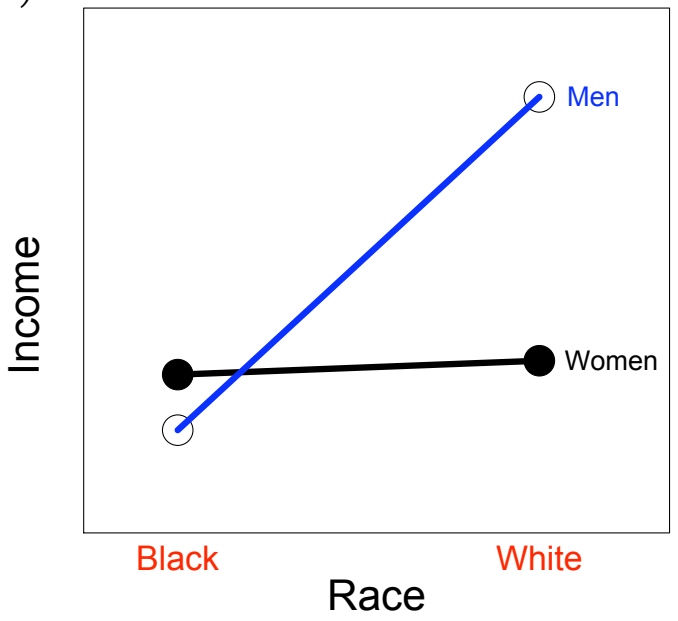
- **Group Analysis: Basic concepts**
  - Variables
    - Dependent: percent signal changes (β's)
    - Independent
      - factors: a categorization (variable) of conditions/tasks/subjects
      - Covariates (IQ, age)
  - Fixed factor
    - Treated as a fixed variable to be estimated in the model
      - Categorization of experiment conditions (mode: Face/House)
      - Group of subjects (male/female, normal/patient)
    - All levels of the factor are of interest and included for replications among subjects
    - Fixed in the sense of inference
      - apply only to the specific levels of the factor, e.g., the response to face/house is well-defined
      - don't extend to other potential levels that might have been included, e.g., the response to face/house doesn't say anything about the response to music

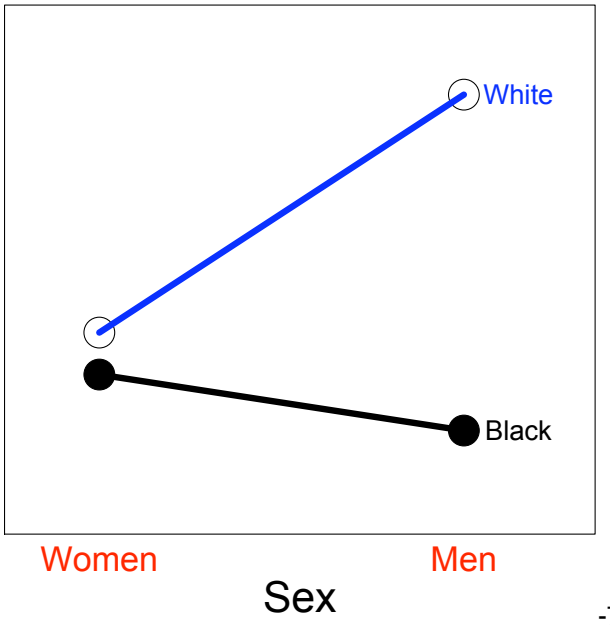
- **Group Analysis: Basic concepts**
  - Random factor
    - Exclusively refers to subject in FMRI
    - Treated as a random variable in the model
      - random effects uniquely attributable to each subject: $N(0, \sigma^2)$: σ^2 to be estimated
    - Each subject is of NO interest
    - Random in the sense of inference
      - subjects serve as a random sample of a population
      - this is why we recruit a lot of subjects for a study
      - inferences can be generalized to a population
      - we usually have to set a long list of criteria when recruiting subjects (right-handed, healthy, age 20-40, native English speaker, etc.)
  - Covariates
    - Confounding/nuisance effects
      - Continuous variables of no interest
      - May cause spurious effects or decrease power if not modeled
      - Some measures about subject: age, IQ, cross-conditions/tasks behavior data, etc.

- **Group Analysis: Types**
  - Fixed: factor, analysis/model/effects
    - Fixed-effects analysis (sometimes): averaging among a few subjects
  - Non-parametric tests
  - Mixed design
    - Mixed design: crossed [e.g., AXBXC] and nested [e.g., BXC(A)]

      Psychologists: Within-subject (repeated measures) / between-subjects factor
  - Mixed-effects analysis (aka random-effects)
    - ANOVA: contains both types of factors: both inter/intra-subject variances
      - Crossed, e.g., AXBXC
      - Nested, e.g., BXC(A)
    - ANCOVA
    - LME
      - Unifying and extending ANOVA and ANCOVA
      - Using ML or ReML

- **Group Analysis: What do we get out of the analysis**
  - Using an intuitive example of income (dependent variable)
    - Factor A: sex (men vs. women)
    - factor B: race (whites vs. blacks)
  - Main effect
    - *F*: general information about all levels of a factor
    - Any difference between two sexes or races
      - men > women; whites > blacks
    - Is it fair to only focus on main effects?
  - Interaction
    - *F*: Mutual/reciprocal influence among 2 or more factors
    - Effect of a factor depends on levels of other factors, e.g.,
      - Black men < black women
      - Black women almost the same as white women
      - Black men << white men
  - General linear test
    - Contrast
    - General linear test (*e.g.*, trend analysis)





- **Group Analysis: Types**
  - Averaging across subjects (fixed-effects analysis)
    - Number of subjects $n < 6$
    - Case study: can't generalize to whole population
    - Simple approach (**3dcalc**)
      - $T = \sum t_{ii}/\sqrt{n}$
    - Sophisticated approach
      - $B = \sum(b_i/\sqrt{v_i})/\sum(1/\sqrt{v_i})$, $T = B\sum(1/\sqrt{v_i})/\sqrt{n}$, v_i = variance for i-th regressor
      - $B = \sum(b_i/v_i)/\sum(1/v_i)$, $T = B\sqrt{[\sum(1/v_i)]}$
      - Combine individual data and then run regression
  - Mixed-effects analysis
    - Number of subjects $n > 10$
    - Random effects of subjects
    - Individual and group analyses: separate
    - Within-subject variation ignored
    - Main focus of this talk

- **Group Analysis: Programs in AFNI**
  - Non-parametric analysis
    - 4 < number of subjects < 10
    - No assumption of normality; statistics based on ranking
    - Programs
      - **3dWilcoxon** (~ paired *t*-test)
      - **3dMannWhitney** (~ two-sample *t*-test)
      - **3dKruskalWallis** (~ between-subjects with **3dANOVA**)
      - **3dFriedman** (~one-way within-subject with **3dANOVA2**)
      - **Permutation test**
    - Multiple testing correction with FDR (**3dFDR**)
    - Less sensitive to outliers (more robust)
    - Less flexible than parametric tests
    - Can't handle complicated designs with more than one fixed factor

- **Group Analysis: Programs in AFNI**
  - Parametric tests (mixed-effects analysis)
    - Number of subjects > 10
    - Assumption: Gaussian random effects
    - Programs
      - **3dttest** (one-sample, two-sample and paired *t*)
      - **3dANOVA** (one-way between-subject)
      - **3dANOVA2** (one-way within-subject, 2-way between-subjects)
      - **3dANOVA3** (2-way within-subject and mixed, 3-way between-subjects)
      - **3dRegAna** (regression/correlation, simple unbalanced ANOVA, simple ANCOVA)
      - **GroupAna** (Matlab package for up to 5-way ANOVA)
      - **3dLME** (R package for all sorts of group analysis)

- **Group Analysis: Planning for mixed-effects analysis**
  - How many subjects?
    - Power/efficiency: proportional to $\sqrt{n}$; $n > 10$
    - Balance: Equal number of subjects across groups if possible
  - Input files
    - Common brain in tlrc space (resolution doesn't have to be 1x1x1 mm^3)
    - Percent signal change (**not** statistics) or normalized variables
      - HRF magnitude: Regression coefficients
      - Linear combinations of β's
  - Analysis design
    - Number of factors
    - Number of levels for each factor
    - Factor types
      - Fixed (factors of interest) vs. random (subject)
      - Cross/nesting: Balanced? Within-subject/repeated-measures vs. between-subjects
    - Which program?
      - **3dttest, 3dANOVA/2/3, GroupAna, 3dRegAna, 3dLME**

• Group Analysis: Planning

- Thresholding
  - Two-tail by default in AFNI
  - If one-tail *p* is desirable, look for 2*p* on AFNI

- Scripting – 3dANOVA3
  - **Three-way between-subjects** (**type 1**)
    - 3 categorizations of groups: sex, disease, age
  - **Two-way within-subject** (**type 4**): Crossed design A×B×C
    - One group of subjects: 16 subjects
    - Two categorizations of conditions: A – category; B - affect
  - **Two-way mixed** (**type 5**): B×C(A)
    - Nesting (between-subjects) factor (A): subject classification, e.g., sex
    - One category of condition (within-subject factor B): condition (visual vs. auditory)
    - Nesting: balanced

• Group Analysis: Example – 2-way within-subject ANOVA

```
3dANOVA3 -type 4  -alevels 3  -blevels 3  -clevels 16 \
-dset 1 1 1 stats.sb04.beta+tlrc'[0]' \
-dset 1 2 1 stats.sb04.beta+tlrc'[1]' \
-dset 1 3 1 stats.sb04.beta+tlrc'[2]' \
-dset 2 1 1 stats.sb04.beta+tlrc'[4]' \
…
-fa  Category \
-fb  Affect \
-fab CatXAff \
-amean    1    T    \ (coding with indices)
-acontr   1 0 -1 TvsF \(coding with coefficients)
-bcontr   0.5 0.5 -1 non-neu \ (coefficients)
-aBcontr  1 -1 0 : 1 TvsE-pos \ (coefficients)
-Abcontr  2 : 1 -1 0 EPosvsENeg \ (coefficients)

-bucket anova33
```

Model type, Factor levels

Input for each cell in ANOVA table: totally 3X3X16 = 144

F tests: Main effects & interaction

t tests: 1st order Contrasts

t tests: 2nd order Contrasts

Output: bundled

- **Group Analysis**: GroupAna
  - Multi-way ANOVA
    - Matlab script package for up to 5-way ANOVA
    - Can handle both volume and surface data
    - Can handle up to 4-way unbalanced designs
      - Unbalanced: unequal number of subjects across groups
      - No missing data from subjects allowed
    - Downsides
      - Requires Matlab plus Statistics Toolbox
      - Slow (minutes to hours): GLM approach - regression through dummy variables
      - Complicated design, and compromised power
    - Solution to heavy duty computation
      - Input with lower resolution recommended
      - Resample with **adwarp -dxyz #** or **3dresample**
    - See http://afni.nimh.nih.gov/sscc/gangc for more info
  - Alternative: **3dLME**

- **Group Analysis**: ANCOVA (ANalysis of COVAriances)
  - Why ANCOVA?
    - Subjects or cross-regressors effects might not be an ideally randomized
    - If not controlled, such variability will lead to loss of power and accuracy
    - Different from amplitude modulation: **cross**-regressors vs. **within**-regressor variation
    - Direct control via design: balanced selection of subjects (e.g., age group)
    - Indirect (statistical) control: add covariates in the model
    - Covariate (variable of no interest): uncontrollable/confounding, usually continuous
      - Age, IQ, cortex thickness
      - Behavioral data, e.g., response time, correct/incorrect rate, symptomatology score, …
  - ANCOVA = Regression + ANOVA
    - Assumption: linear relation between HDR and the covariate
    - GLM approach: accommodate both categorical and quantitative variables
  - Programs
    - **3dRegAna**: for simple ANCOVA
      - If the analysis can be handled with 3dttest without covariates
      - See http://afni.nimh.nih.gov/sscc/gangc/ANCOVA.html for more information
    - **3dLME**: R package

• Group Analysis: 3dLME

- Linear regression vs. Linear mixed-effects (or hierarchical)
  - R package: Open source platform
  - Versatile: handles almost all situations in one package
    - Unbalanced designs (unequal number of subjects, missing data, etc.)
    - ANOVA and ANCOVA, but unlimited number of factors and covariates
    - Able to handle HRF modeling with basis functions
    - Violation of sphericity: heteroscedasticity, variance-covariance structure
    - Model fine-tuning
  - No scripting (input is bundled into a text file model.txt)
  - Disadvantages
    - High computation cost (lots of repetitive calculation)
    - Sometimes difficult to compare with traditional ANOVA
  - See http://afni.nimh.nih.gov/sscc/gangc/lme.html for more information

- **Group Analysis**: 3dLME
  - Linear (Regression) model
    - $y_i = \beta_0 + \beta_1 x_{1i} + \ldots + \beta_p x_{pi} + \varepsilon_i$, $\varepsilon_i \sim N(0, \sigma^2)$, for ith subject
    - $Y = X\beta + \varepsilon$, $\varepsilon \sim \mathrm{N}_n(0, \sigma^2 \Lambda_n)$, for each subject
    - Only one random-effect compoent, residual ε
  - Linear mixed-effects (LME) model
    - $y_{ij} = \beta_0 + \beta_1 x_{1ij} + \ldots + \beta_p x_{pij} + b_{i1} z_{1ij} + \ldots + b_{iq} z_{qij} + \varepsilon_{ij}$,
      $b_{ik} \sim \mathrm{N}(0, \psi_k^2)$, $\mathrm{cov}(b_k, b_{k'}) = \psi_{kk'}$, $\varepsilon_{ij} \sim N(0, \sigma^2 \lambda_{ijj})$, $cov(\varepsilon_{ij}, \varepsilon_{ij'}) = \sigma^2 \lambda_{ijj'}$
    - $Y_i = X_i\beta + Z_i b_i + \varepsilon_i$, $b_i \sim N_q(0, \psi)$, $\varepsilon_i \sim N_{n_i}(0, \sigma^2 \Lambda_i)$, for ith subject
    - Two random-effect components: $Z_i b_i$ nd ε_i
    - AN(C)OVA can be incorporated as a special case
      - n_i is constant (>1, repeated-measures), $\Lambda_i = I_{n \times n}$ (iid)

• Group Analysis: 3dLME

Running LME

↙ Create a text file model.txt (3 fixed factors plus 1 covariate)

```
Data:Volume                              <-- either Volume or Surface
Output:FileName                          <-- any string (no suffix needed)
MASK:Mask+tlrc.BRIK                      <-- mask dataset
Model:Age+Gender*Object*Modality         <-- model formula for fixed effects
COV:Age                                  <-- covariate list
RanEff:1                                 <-- random effects
VarStr:0
CorStr:0
Clusters:4                              <-- number of parallel jobs
SS:sequential
MFace-FFace                             <-- contrast label
Male*Face*0*0-Female*Face*0*0           <-- contrast specification
MVisual-Maudial
Male*0*Visual*0-Male*0*Audial*0
......
Subj      Gender          Object          Modality     Age    InputFile
Jim       Male            Face            Visual       25     file1+tlrc.BRIK
Carol     Female          House           Audial       23     file2+tlrc.BRIK
Karl      Male            House           Visual       26     file3+tlrc.BRIK
Casey     Female          Face            Audial       24     file4+tlrc.BRIK
......
```

↙ Run 3dLME.R MyOut &

- **Group Analysis**: 3dLME
  - HRF modeled with basis functions
    - Traditional approach: AUC
      - Hard to detect shape difference
      - Difficult to handle betas with mixed signs
    - LME approach
      - Usually H_0: $\beta_1=\beta_2=\ldots=\beta_k$ (not H_0: $\beta_1=\beta_2=\ldots=\beta_k=0$)
      - But now we don't care about the differences among β's
      - Instead we want to detect shape difference
      - Solution: take all β's and model with no intercept
      - But we have to deal with temporal correlations among β's, $\Lambda_i \neq I_{n\text{x}n}$
      - For example, AR(1): 2 parameters σ^2 and ρ for the residuals

$$\sigma^2\Lambda_i = \begin{pmatrix} \sigma^2 & \sigma^2\rho & \ldots & \sigma^2\rho^{n_i-1} \\ \sigma^2\rho & \sigma^2 & \ldots & \sigma^2\rho^{n_i-2} \\ \vdots & \vdots & \ddots & \vdots \\ \sigma^2\rho^{n_i-1} & \sigma^2\rho^{n_i-2} & \ldots & \sigma^2 \end{pmatrix}$$

- **Group Analysis**: 3dLME
  - Running LME: A more complicated example
    - HRF modeled with 6 tents
    - Null hypothesis: no HRF difference between two conditions

```
Data:Volume                                  <-- either Volume or Surface
Output:test                                  <-- any string (no suffix needed)
MASK:Mask+tlrc.BRIK                          <-- mask dataset
Model:Time-1                                 <-- model formula for fixed effects
COV:                                         <-- covariate list
RanEff:1                                     <-- random effect specification
VarStr:0                                     <-- heteroscedasticity?
CorStr:1~TimeOrder|Subj                      <-- correlation structure
SS: sequential                               <-- sequential or marginal
Clusters:4                                   <-- number of parallel jobs
Subj     Time    TimeOrder  InputFile
Jim      t1        1   contrastT1+tlrc.BRIK
Jim      t2        2   contrastT2+tlrc.BRIK
Jim      t3        3   contrast3+tlrc.BRIK
......
```

    - Output: F for H_0, β and t for each basis function

- **Group Analysis**: 3dttest might be your good friend!
  - Example: 2-way mixed ANOVA with unequal subjects
    - Can't use 3dANOVA3 –type 5
    - All the *t* tests can be done with 3dttest
    - Even main effects and interaction can be obtained for 2×2 design
    - A: Gender (M vs. F, between-subject); B: stimulus (House vs. Face, within-subject)
    - Group difference on House: two-sample *t*-test

```
3dttest -set1 Male1House …  -set2 Female1House … -prefix GroupHDiff
```

    - Gender main effect

```
3dcalc -a Suject1House -b Subject1Face -expr 'a+b' -prefix Subject1H+F
```

(Or `3dMean -prefix Subj1CaT Suject1House Subject1Face`)

```
3dttest -set1 Male1H+F … -set2 Female1H+F -prefix HouseEff
```

    - Interaction between Gender and Stimulus

```
3dcalc -a Suject1House -b Subject1Face -expr 'a-b' -prefix Subject1HvsF
3dttest -set1 Male1HvsF … -set2 Female1HvsF -prefix Interaction
```

Multi-Voxel Statistics

Spatial Clustering

&

False Discovery Rate:

"Correcting" the Significance

Multiple Testing Corrections

- **Two types of errors**
  - What is **H_0** in FMRI studies? H_0: no effect (activation, difference, …) at a voxel
  - Type I error = Prob(reject H_0 when H_0 is true) = false positive = p value

    Type II error = Prob(accept H_0 when H_1 is true) = false negative = β

    power = $1-\beta$ = probability of detecting true activation
  - Strategy: control type I error while increasing power (decreasing type II errors)
  - Significance level α (magic number 0.05) : $p < \alpha$

Justice System: Trial

Hidden Truth

	Defendant Innocent	Defendant Guilty
Reject Presumption of Innocence (Guilty Verdict)	**Type I Error** (defendant very unhappy)	**Correct**
Fail to Reject Presumption of Innocence (Not Guilty Verdict)	**Correct**	**Type II Error** (defendant very happy)

Statistics: Hypothesis Test

Hidden Truth

	H_0 True Not Activated	H_0 False Activated
Reject H_0 (decide voxel is activated)	**Type I Error** (false positive)	**Correct**
Don't Reject H_0 (decide voxel isn't activated)	**Correct**	**Type II Error** (false negative)

• Cluster Analysis: Multiple testing correction

Family-Wise Error (FWE)

- Birth rate H_0: sex ratio at birth = 1:1
  - What is the chance there are 5 boys (or girls) in a family? $(1/2)^5 \sim 0.03$
  - In a pool of 10000 families with 5 kids, expected #families with 5 boys =? $10000X(2)^5 \sim 300$
- Multiple testing problem: voxel-wise statistical analysis
  - With n voxels, what is the chance to mistake ≥ one voxel?

    Family-Wise Error: $\alpha_{FW} = 1-(1- p)^n \rightarrow 1$ as n increases
  - $n \sim$ 20,000-100,000 voxels in the brain

Multiple testing problem in FMRI

- 3 occurrences of multiple tests: individual, group, and conjunction
- Group analysis is the most concerned

• Cluster Analysis: Multiple testing correction

Approaches

↙ Control FWE

- ➢ Overall significance: $\alpha_{FW} = P$ (≥ one false positive voxel in the whole brain)
- ➢ Bonferroni correction: $\alpha_{FW} = 1-(1- p)^n \sim np$, if $p << 1/n$
  - * Use $p=\alpha/n$ as individual voxel significance level to achieve $\alpha_{FW} = \alpha$
  - * Too stringent and overly conservative: $p=10^{-8}\sim10^{-6}$
- ➢ Something to rescue?
  - * Correlation: Voxels in the brain are not independent
  - * Cluster: Structures in the brain
  - * Control FWE based on spatial correlation and cluster size

↙ Control false discovery rate (FDR)

- ➢ FDR = expected proportion of false + voxels among all detected voxels

- **Cluster Analysis**: **`AlphaSim`**
  - FWE in AFNI
    - Monte Carlo simulations with **`AlphaSim`**
    - Named for Monte Carlo, Monaco, where the primary attractions are casinos
    - Program: **`AlphaSim`**
      - Randomly generate some number (*e.g.*, 1000) of brains with white noise
      - Count the proportion of voxels are false + in **ALL** (*e.g.*, 1000) brains
      - Parameters:
        * ROI - mask
        * Spatial correlation - FWHM
        * Connectivity – radium: how to identify voxels belong to a cluster?
        * Individual voxel significant level - uncorrected *p*
      - Output
        * Simulated (estimated) overall significance level (corrected *p*-value)
        * Corresponding minimum cluster size

- **Cluster Analysis**: **AlphaSim**
  - Program: **AlphaSim**
    - See detailed steps at http://afni.nimh.nih.gov/sscc/gangc/mcc.html
    - Example

```
AlphaSim \
-mask MyMask+orig \
-fwhmx 8.5 -fwhmy 7.5 -fwhmz 8.2 \
-rmm 6.3 \
-pthr 0.0001 \
-iter 1000
```

Program

Restrict correcting region: ROI

Spatial correlation

Connectivity: how clusters are defined

Uncorrected *p*

Number of simulated brains

    - Output: 5 columns
      * Focus on the 1st and last columns, and ignore others
      * 1st column: minimum cluster size in voxels
      * Last column: alpha (α), overall significance level (corrected *p* value)

Cl Size	Frequency	Cum Prop	p/Voxel	Max Freq	Alpha
2	1226	0.999152	0.00509459	831	0.859
5	25	0.998382	0.00015946	25	0.137
10	3	1.0	0.00002432	3	0.03

    - May have to run several times with different uncorrected *p*

      uncorrected p ↑ ↔ cluster size ↑

• Cluster Analysis: 3dFDR

	Declared Inactive	Declared Active	
Truly Inactive	N_{ii}	N_{ia} (*I*)	T_i
Truly Active	N_{ai} (*II*)	N_{aa}	T_a
	D_i	D_a	

- Definition

  FDR = % false + voxels among all detected voxels in **ONE** brain

$$FDR = \frac{N_{ia}}{D_a} = \frac{N_{ia}}{N_{ia} + N_{aa}}$$

  - FDR only focuses on individual voxel's significance level within the ROI, but doesn't consider any spatial structure
    - spatial correlation
    - cluster size

- Algorithm
  - statistic (*t*) ➔ *p* value ➔ FDR (*q* value) ➔ *z* score

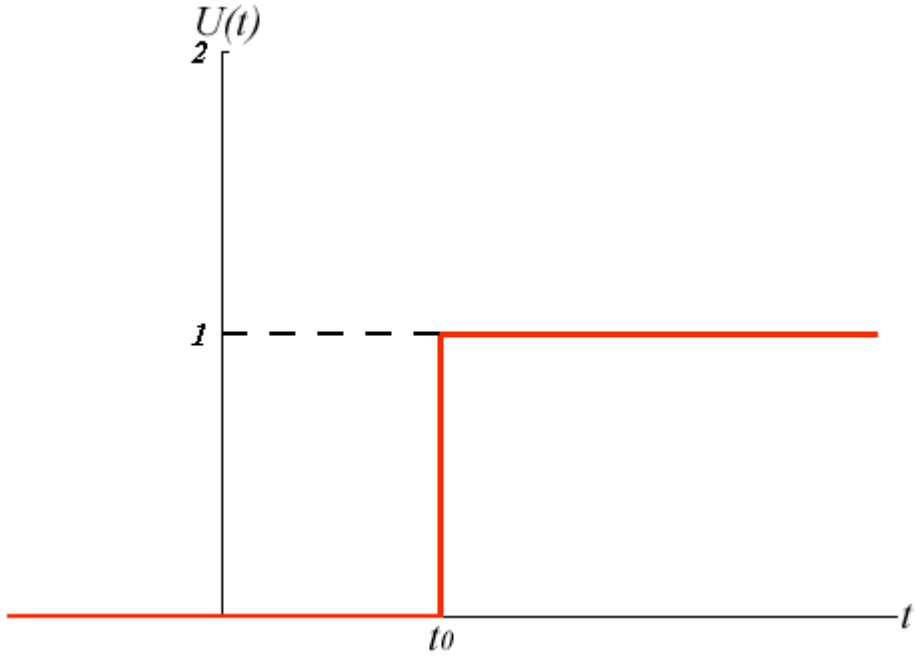
- 3dFDR is obsolete
  - Most programs automatically provide *q* values
  - If not, run 3drefit –addFDR

- **Cluster Analysis**: FWE or FDR?
  - FWE or FDR? Correct type I error in different sense
    - FWE: $\alpha_{FW} = P$ (≥ one false positive voxel in the whole brain)
      - Frequentist's perspective: Probability among many hypothetical activation brains
      - Used usually for parametric testing
    - FDR = expected % false + voxels among all detected voxels
      - Focus: controlling false + among detected voxels in one brain
      - More frequently used in non-parametric testing
    - Concrete example
      - Individual (uncorrected) voxel $p = 0.001$ for a brain of 25,000 EPI voxels
      - Uncorrected → 25 false + voxels in the brain
      - FWE: corrected $p = 0.05$ → 5% false + hypothetical brains for a fixed voxel location
      - FDR: corrected $p = 0.05$ → 5% voxels in those positively labeled ones are false +
  - Fail to survive correction?
    - Tricks
      - One-tail?
      - ROI – e.g., grey matter or whatever anatomical ROI you planned to look into
    - Analysis on surface

- **Cluster Analysis**: Conjunction analysis
  - Conjunction analysis
    - Common activation area: intersection
    - Exclusive activations
    - With *n* entities, we have 2^n possibilities (review your combinatorics!)
  - Tool: `3dcalc`
    - Heaviside unit (step function)

      defines a *On/Off* event

$$U(t-t_0) = \begin{cases} 1 & t \geq t_0 \\ 0 & t < t_0 \end{cases}$$



- **Cluster Analysis**: Conjunction analysis
  - Example
    - 3 contrasts A, B, and C
    - Assign each based on binary system: A: 001(2^0=1); B: 010(2^1=2); C: 100(2^2=4)
    - Create a mask with 3 sub-bricks of *t* (*e.g.*, threshold = 4.2)

```
3dcalc -a ContrA+tlrc -b ContrB+tlrc -c ContrC+tlrc \
-expr '1*step(a-4.2)+2*step(b-4.2)+4*step(c-4.2)'   \
-prefix ConjAna
```

    - Interpret output - 8 (=2^3) scenarios:

000(0): none;

001(1): A but no others;

010(2): B but no others;

011(3): A and B but not C;

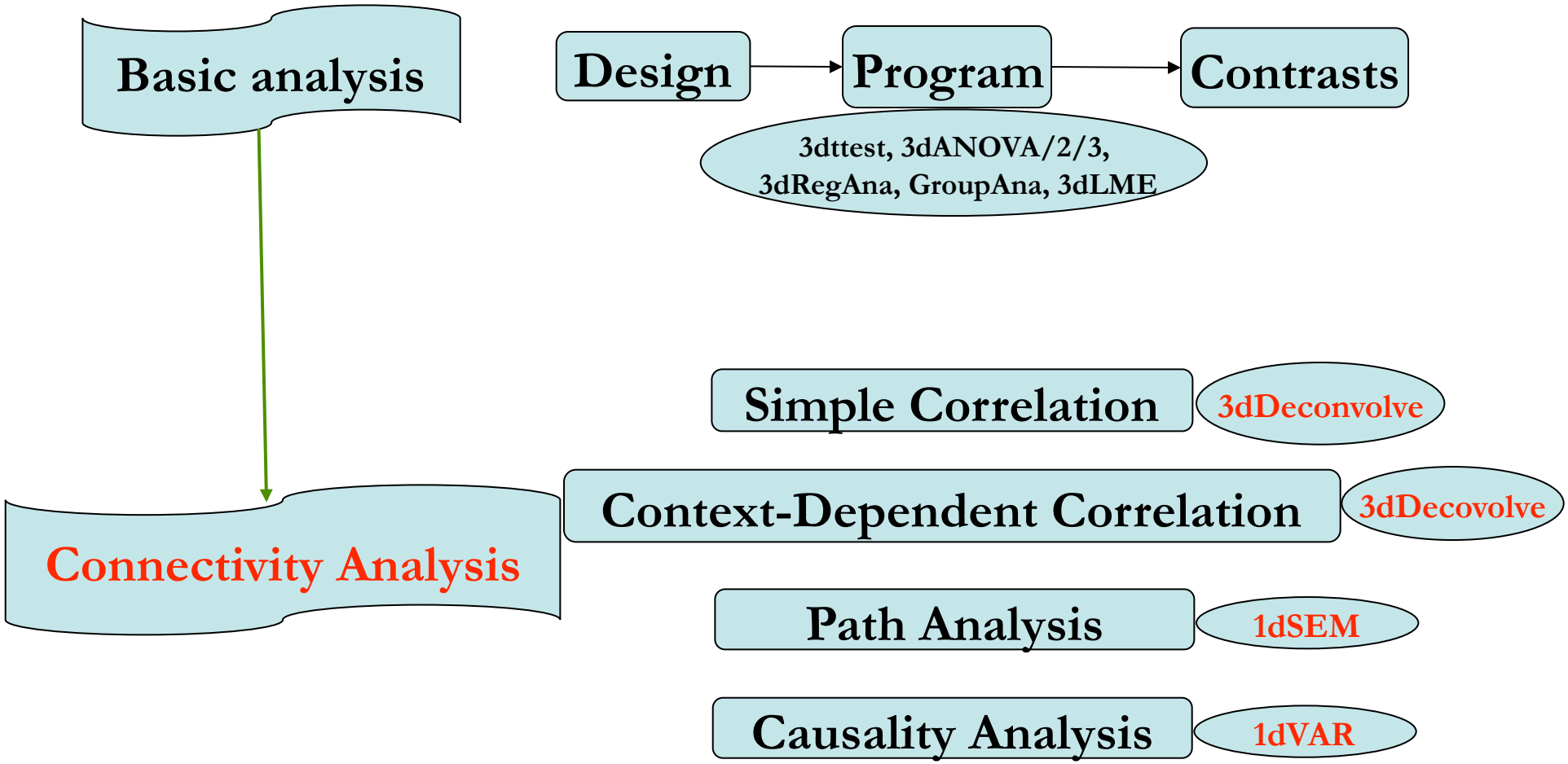
100(4): C but no others;

101(5): A and C but not B;

110(6): B and C but not A;

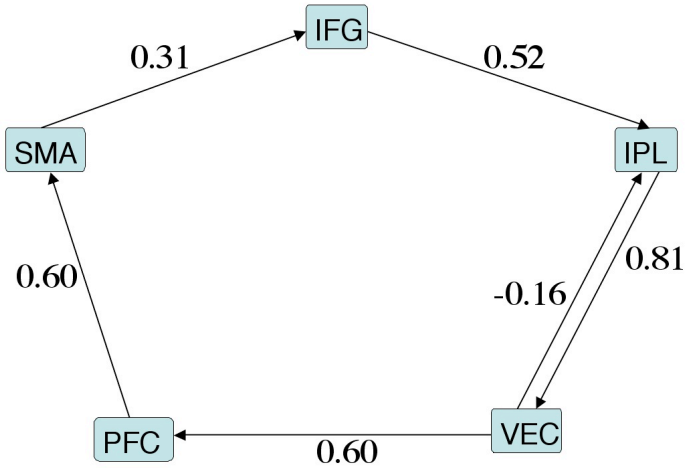
111(7): A, B and C

Group Analysis



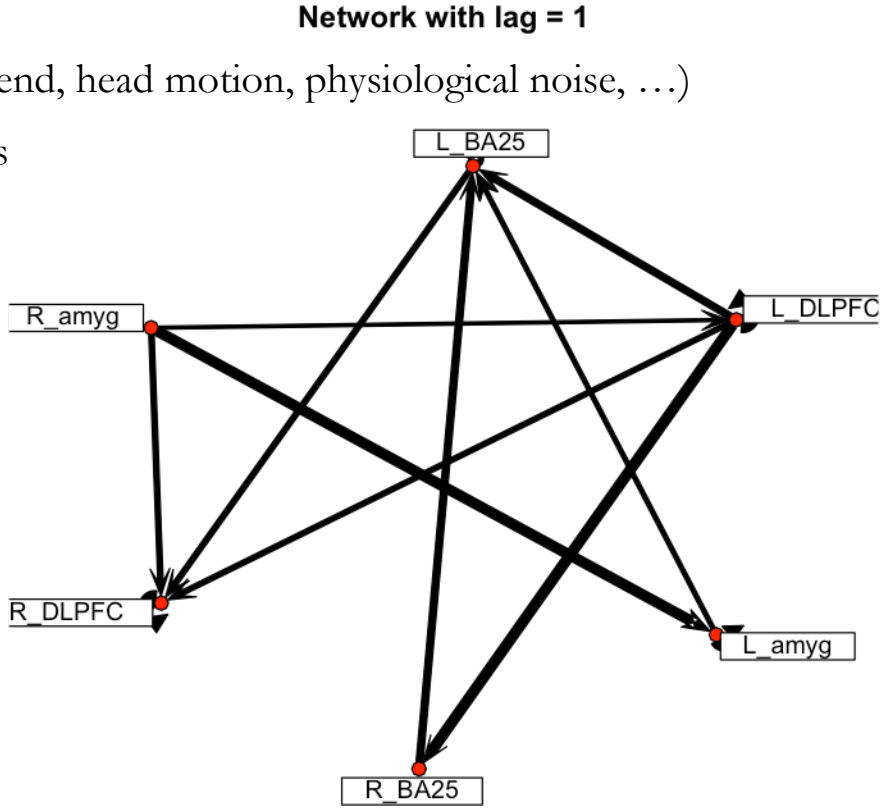
- **Connectivity: Correlation Analysis**
  - Correlation analysis (aka functional connectivity)
    - Similarity between a seed region and the rest of the brain
    - Says not much about causality/directionality
    - Voxel-wise analysis; Both individual subject and group levels
    - Two types: simple and context-dependent correlation (a.k.a. PPI)
  - Steps at individual subject level
    - Create ROI (a sphere around peak t-statistic or an anatomical structure)
    - Isolate signal for a condition/task
    - Extract seed time series
    - Run correlation analysis through regression analysis
    - More accurately, partial (multiple) correlation
  - Steps at group level
    - Convert correlation coefficients to *Z* (Fisher transformation): 3dcalc
    - One-sample *t* test on *Z* scores: `3dttest`
  - Interpretation, interpretation, interpretation!!!
    - Correlation doesn't mean causation or/and anatomical connectivity
    - Be careful with group comparison!

- **Connectivity: Path Analysis or SEM**
  - Causal modeling (a.k.a. structural or effective connectivity)
    - Start with a network of ROI's
    - Path analysis
      - Assess the network based on correlations (covariances) of ROI's
      - Minimize discrepancies between correlations based on data and estimated from model
      - Input: Model specification, correlation matrix, residual error variances, DF
      - Output: Path coefficients, various fit indices
    - Caveats
      - H_0: It is a good model; Accepting H_0 is usually desirable
      - Valid only with the data and model specified
      - No proof: modeled through correlation analysis
      - Even with the same data, an alternative model might be equally good or better
      - If one critical ROI is left out, things may go awry
      - Interpretation of path coefficient: NOT correlation coefficient, possible >1



- **Connectivity: Path Analysis or SEM**
  - Path analysis with **1dSEM**
    - Model validation: 'confirm' a theoretical model
      - Null hypothesis: good model! Accept, reject, or modify the model?
    - Model search: look for 'best' model
      - Start with a minimum model (1): can be empty
      - Some paths can be excluded (0), and some optional (2)
      - Model grows by adding one extra path a time
      - 'Best' in terms of various fit criteria
    - More information http://afni.nimh.nih.gov/sscc/gangc/PathAna.html
  - Difference between causal and correlation analysis
    - Predefined network (model-based) vs. network search (data-based)
    - Modeling: causation (and directionality) vs. correlation
    - ROI vs. voxel-wise
    - Input: correlation (condensed) vs. original time series
    - Group analysis vs. individual + group

- **Connectivity: Granger Causality or VAR**
  - Causal modeling (a.k.a. structural or effective connectivity)
    - Start with a network of ROI's
    - Causality analysis through vector auto-regressive modeling (VAR)
      - Assess the network based on correlations of ROIs' time series
      - If values of region *X* provide statistically significant information about future values of *Y*, *X* is said to Granger-cause *Y*
      - Input: time series from ROIs, covariates (trend, head motion, physiological noise, …)
      - Output: Path coefficients, various fit indices
  - Causality analysis with **1dGC**
    - Written in R
    - Can run both interactive and batch mode
    - Generate a network and path matrix
    - A list of model diagnostic tests
    - Run group analysis on path coefficients
  - Causality analysis with **3dGC**
    - Seed vs. whole brain



- **Connectivity: Granger Causality or VAR**
  - Causal modeling (a.k.a. structural or effective connectivity)
    - Caveats
      - It has assumptions (stationary property, Gaussian residuals, and linearity)
      - Require accurate region selection: missing regions may invalidate the analysis
      - Sensitive to number of lags
      - Time resolution
      - No proof: modeled through statistical analysis
      - Not really cause-effect in strict sense
      - Interpretation of path coefficient: temporal correlation
  - SEM versus VAR
    - Predefined network (model-based) among ROIs
    - Modeling: statistical causation (and directionality)
    - Input: correlation (condensed) vs. original time series
    - Group analysis vs. individual + group

- **Connectivity: Granger Causality or VAR**
  - Why temporal resolution is important?